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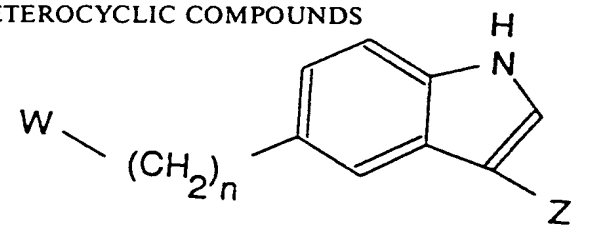

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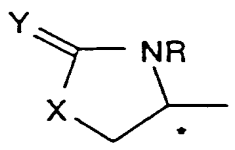

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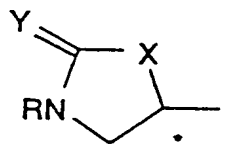

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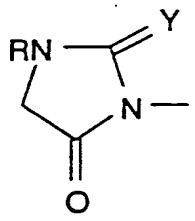

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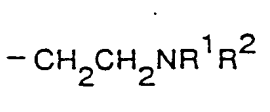


(iv)

(v)

(vi)

(57) Abstract

The present invention is concerned with compounds of formula (I), wherein n is an integer of from 0 to 3; W is a group of formula (i), (ii), or (iii), wherein R is hydrogen or C_{1-4} alkyl, X is -O-, -S-, -NH-, or $-CH_2-$, Y is oxygen or sulphur and the chiral centre (*) in formula (i) or (ii) is in its (S) or (R) form or is a mixture thereof in any proportions; and Z is a group of formula (iv), (v), or (vi), wherein R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl and R^3 is hydrogen or C_{1-4} alkyl; and their salts, solvates and physiologically functional derivatives, with processes for their preparation, with medicaments containing them and with their use as therapeutic agents, particularly in the prophylaxis and treatment of migraine.

THERAPEUTIC HETEROCYCLIC COMPOUNDS

The present invention is concerned with new chemical compounds, their preparation, pharmaceutical formulations containing them and their use in medicine, particularly the prophylaxis and treatment of migraine.

Receptors which mediate the actions of 5-hydroxytryptamine (5-HT) have been identified in mammals in both the periphery and the brain. According to the classification and nomenclature proposed in a recent article (Bradley et al, Neuropharmac., 25, 563 (1986)), these receptors may be classified into three main types, viz. "5-HT_1-like", 5-HT_2 and 5-HT_3. Various classes of compounds have been proposed as 5-HT agonists or antagonists for therapeutic use, but these have not always been specific to a particular type of 5-HT receptor. European Patent Specification 0313397 describes a class of 5-HT agonists which are specific to a particular type of "5-HT_1-like" receptor and are effective therapeutic agents for the treatment of clinical conditions in which a selective agonist for this type of receptor is indicated. For example, the receptor in question mediates vasoconstriction in the carotid vascular bed and thereby modifies blood flow therein. The compounds described in the European specification are therefore beneficial in the treatment or prophylaxis of conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example, migraine, a condition associated with excessive dilation of the carotid vasculature. However, it is within the scope of the earlier application that the target tissue may be any tissue wherein action is mediated by "5-HT_1-like" receptors of the type referred to above.

We have now found a further class of compounds having exceptional "5-HT_1-like" receptor agonism and excellent absorption following oral dosing. These properties render the compounds particularly useful for certain medical applications, notably the prophylaxis and treatment of migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as "migraine".

wherein R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl and R^3 is hydrogen or C_{1-4} alkyl;

and salts, solvates and physiologically functional derivatives thereof.

Compounds of formula (I) having particularly desirable properties for the treatment and prophylaxis of migraine include those wherein n is 1, W is a group of formula (i) and Z is a group of formula (iv) or (vi). Of these, compounds of formula (I) wherein n is 1, W is a group of formula (i) wherein R is hydrogen, X is -O- and Y is oxygen and Z is a group of formula (iv) or (vi) wherein R^1 = R^2 = hydrogen or methyl are particularly preferred.

Two compounds of formula (I) having exceptional properties for the treatment and prophylaxis of migraine are N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine and 3-(1-methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole in either their (S) or (R) form or as a mixture thereof in any proportions. The salts and solvates of these compounds, for example, the hydrate maleates, are particularly preferred.

Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, ie basic, compounds. Such salts must clearly have a physiologically acceptable anion. Suitable physiologically acceptable salts of the compounds of the present invention include those derived from acetic, hydrochloric, hydrobromic, phosphoric, malic, maleic, fumaric, citric, sulphuric, lactic, or tartaric acid. The succinate and chloride salts are particularly preferred for medical purposes. Salts having a non-physiologically acceptable anion are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, in vitro, situations.

ingredient, at least one compound of formula (I) and/or a pharmacologically acceptable salt or solvate thereof together with at least one pharmaceutical carrier or excipient. These pharmaceutical compositions may be used in the prophylaxis or treatment of clinical conditions for which a "5-HT_1-like" receptor agonist is indicated, for example, migraine. The carrier must be pharmaceutically acceptable to the recipient and must be compatible with, i.e. not have a deleterious effect upon, the other ingredients in the composition. The carrier may be a solid or liquid and is preferably formulated with at least one compound of formula (I) as a unit dose formulation, for example, a tablet which may contain from 0.05 to 95% by weight of the active ingredient. If desired, other physiologically active ingredients may also be incorporated in the pharmaceutical compositions of the invention.

Possible formulations include those suitable for oral, sublingual, buccal, parenteral (for example, subcutaneous, intramuscular, or intravenous), rectal, topical and intranasal administration. The most suitable means of administration for a particular patient will depend on the nature and severity of the condition being treated and on the nature of the active compound, but, where possible, oral administration is preferred.

Formulations suitable for oral administration may be provided as discrete units, such as tablets, capsules, cachets, or lozenges, each containing a predetermined amount of the active compound; as powders or granules; as solutions or suspensions in aqueous or non-aqueous liquids; or as oil-in-water or water-in-oil emulsions.

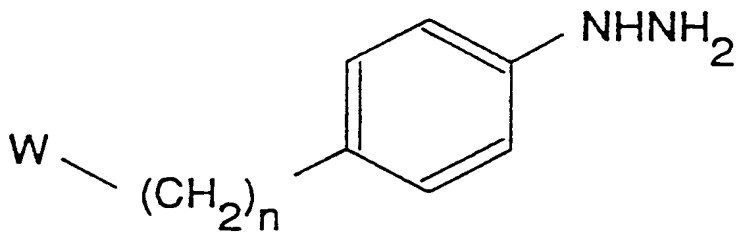
Formulations suitable for sublingual or buccal administration include lozenges comprising the active compound and, typically, a flavoured base, such as sugar and acacia or tragacanth, and pastilles comprising the active compound in an inert base, such as gelatin and glycerin or sucrose and acacia.

desired concentration and then rendering the resulting solution sterile and isotonic.

Thus, according to a fourth aspect of the present invention, there is provided the use of a compound of formula (I) in the preparation of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated, for example, migraine.

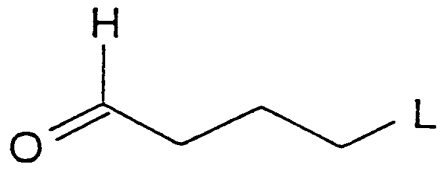
According to a fifth aspect, there is provided a method for the prophylaxis or treatment of a clinical condition in a mammal, for example, a human, for which a "5-HT_1-like" receptor agonist is indicated, for example, migraine, which comprises the administration to said mammal of a therapeutically effective amount of a compound of formula (I) or of a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

According to a sixth aspect of the invention, compounds of formula (I) wherein Z is a group of formula (iv) may be prepared by reacting a compound of formula (II) (isolated or *in situ* - *infra*).



(II)

wherein n and W are as hereinbefore defined, with a compound of formula (III)



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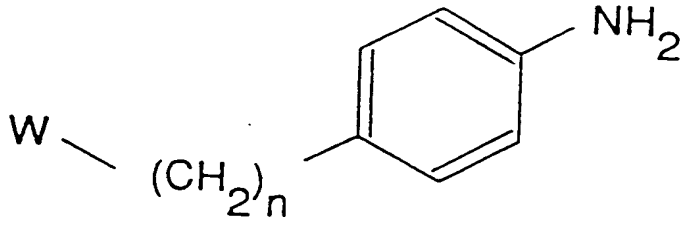
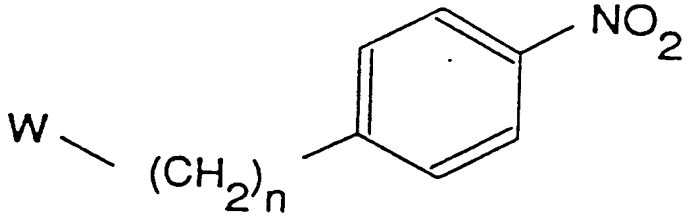


(IV)

wherein n and W are as hereinbefore defined, by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/c.HCl and the resulting diazo product reduced in situ using, for example, tin(II) chloride/c.HCl. The resulting hydrazine may be isolated or converted to a compound of formula (I) in situ.

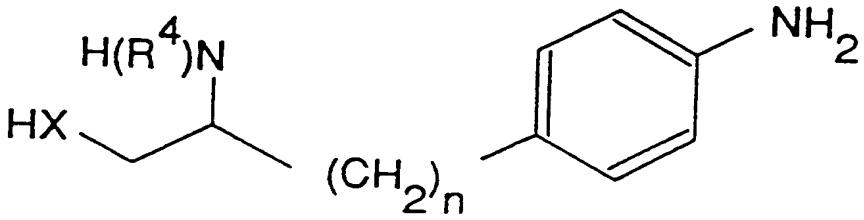
Anilines of formula (IV) may be prepared by reduction of the corresponding p-nitro compound of formula (V)



(V)

wherein n and W are as hereinbefore defined, typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent system, such as an acidified mixture of ethanol, water and ethyl acetate.

Anilines of formula (IV) wherein W is a group of formula (i) or (ii) may also be prepared by cyclising a compound of formula (XXXIII)

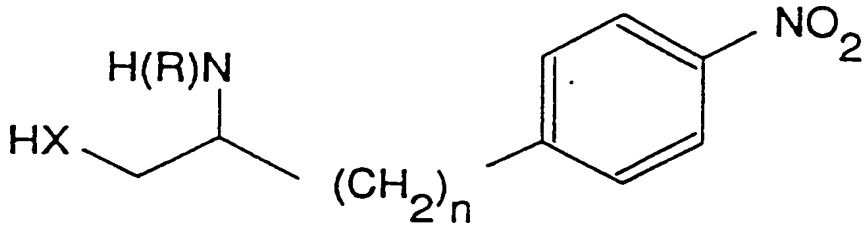


(XXXIII)

hydrogenation using, for example, Pd/C in a polar solvent, such as ethanol. The dinitro compound may be prepared by reacting the appropriate aldehyde with nitromethane, typically in the presence of a base, for example, sodium methoxide, in a polar solvent, such as methanol, followed by p-nitration using, for example, $c.H_2SO_4/c.HNO_3$, or by p-nitration of the appropriate aldehyde followed by reaction with nitromethane. The aldehyde may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

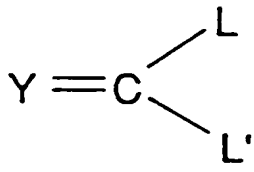
p-Nitro compounds of formula (V) may be prepared by

(a) in the case where W is a group of formula (i) in which Y is oxygen or sulphur, reacting a compound of formula (VI)



(VI)

wherein n, R and X are as hereinbefore defined, with a compound of formula (VII)



(VII)

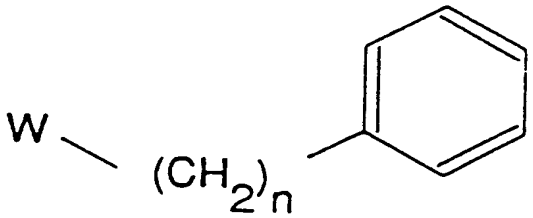
wherein Y is as hereinbefore defined and L and L', which may be the same or different, are suitable leaving groups, for example, chlorine, ethoxy, trichloromethyl, trichloromethoxy, or imidazoyl, for example, in the case where L = L' = chlorine, in a non-polar solvent, such as toluene, in the presence of a base, for example, potassium hydroxide.

Compounds of formula (VI) wherein X is oxygen may be prepared by esterification of the corresponding carboxylic acid, typically by treatment with thionyl chloride and an appropriate alcohol at -10°C, followed by reduction of the ester using, for example, sodium borohydride, in a polar solvent system, such as ethanol/water, at 0°C. The acid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature, for example, by p-nitration of the corresponding aminoacid using, for example, $c.H_2SO_4/c.HNO_3$ at 0°C.

Compounds of formula (VIII) may be prepared by ring-opening a compound of formula (V) wherein n is a hereinbefore defined and W is a group of formula (ii) in which R, X and Y are as hereinbefore defined, for example, by refluxing in 2N aqu. KOH.

Compounds of formula (III), (VII), (IX) and (X) may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

p-Nitro compounds of formula (V) wherein W is a group of formula (i) or (ii) may also be prepared by p-nitration of a compound of formula (XXXVI)



(XXXVI)

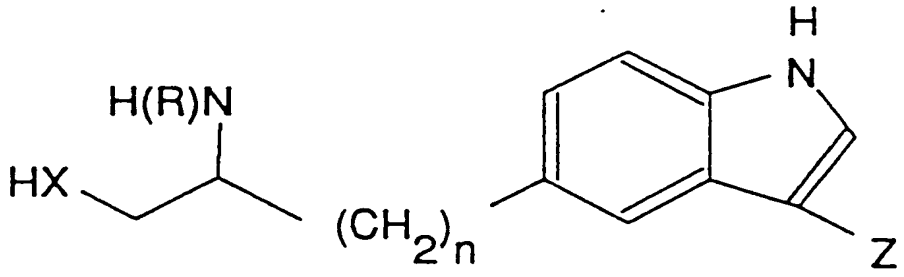
wherein n and W are as hereinbefore defined, using, for example, $c.H_2SO_4/c.HNO_3$ at 0°C.

Compounds of formula (XXXVI) may be prepared by reacting a compound of formula (XXXVII)

appropriate aldehyde with nitromethane, typically in the presence of a base, for example, sodium methoxide, in a polar solvent, such as methanol. The compound of formula (XXIV), the acid and the aldehyde may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

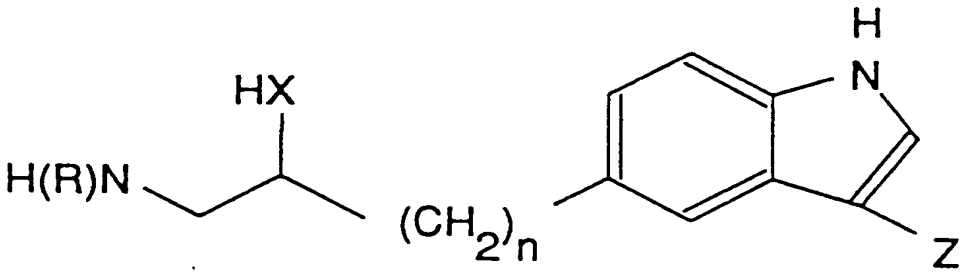
p-Nitro compounds of formula (V) wherein W is a group of formula (i), (ii), or (iii) in which R is C_{1-4} alkyl may be prepared from the corresponding compound of formula (V) wherein R is hydrogen by N-alkylation using a suitable agent, such as the appropriate dialkyl sulphate, typically in the presence of a base, for example, sodium hydride, in a non-polar solvent, such as THF.

Compounds of formula (I) wherein W is a group of formula (i) or (ii) may also be prepared by reacting a compound of formula (XV)



(XV)

or (XXV)

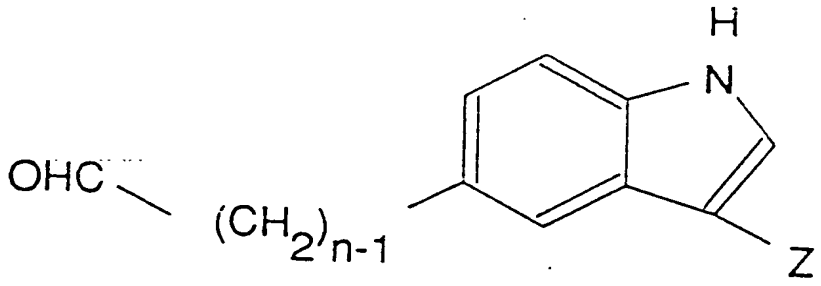


(XXV)

wherein n, R, X and Z are as hereinbefore defined, with a compound of formula (VII) wherein Y, L and L' are as hereinbefore defined, for example, in the case where L = L' = ethoxy, by heating in the presence of a base, for example, potassium carbonate.

system, such as ethanol/water. Alternatively, an enantioselective reducing agent, such as Rh(cod)(dipamp)$^+BF_4^-$ (JCS. Chem. Comm. 275 (1991)), may be used to reduce the double bond and thereby introduce a chiral centre at the 4-position of the dioxoimidazole ring. The reduction step may be used to convert a compound of formula (XVII) wherein Z is a group of formula (v) into a compound of formula (XVI) wherein Z is a group of formula (vi).

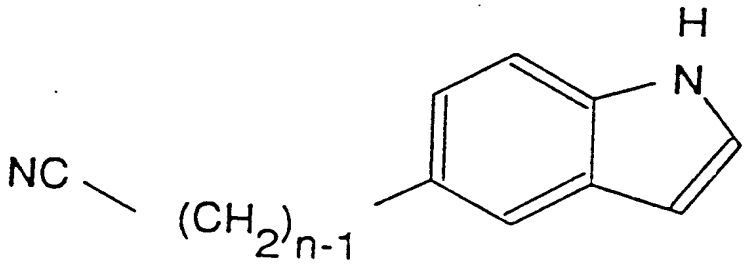
Compounds of formula (XVII) may be prepared by reacting a compound of formula (XVIII)



(XVIII)

wherein n and Z are as hereinbefore defined, with, in the case where R^6 is to be hydrogen, a compound of formula (X) wherein R is as hereinbefore defined, typically by heating in glac. acetic acid in the presence of ammonium acetate.

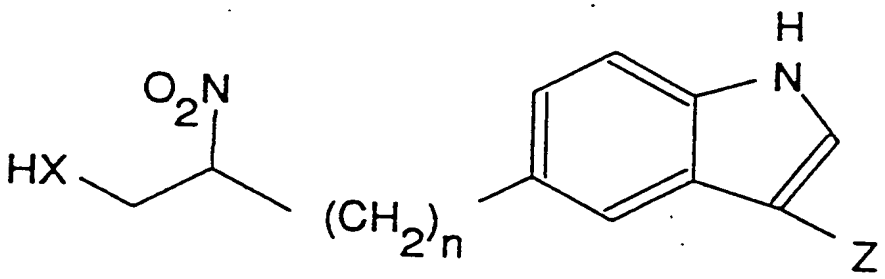
Compounds of formula (XVIII) may be prepared by the reduction/hydrolysis of the corresponding nitrile, typically using Raney nickel and sodium hypophosphite in a mixture of water, acetic acid and pyridine. The nitrile may be prepared by reacting a compound of formula (XIX)



(XIX)

Hydrazines of formula (XXXV) may be prepared from the corresponding aniline, typically using the reaction conditions described above for the conversion of (IV) to (II). The aniline may be prepared by reducing the corresponding p-nitro compound, typically using the reaction conditions described above for the conversion of (V) to (IV). The p-nitro compound may be prepared by reacting the corresponding p-nitroaminoacid with benzyl isocyanate in the presence of base, for example, potassium hydroxide, in a polar solvent, such as water. The p-nitroaminoacid may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature, for example, by p-nitration of the corresponding aminoacid using, for example, $c.H_2SO_4/c.HNO_3$ at 0^oC.

Compounds of formula (XV) wherein R is hydrogen may be prepared by reducing a compound of formula (XX)



(XX)

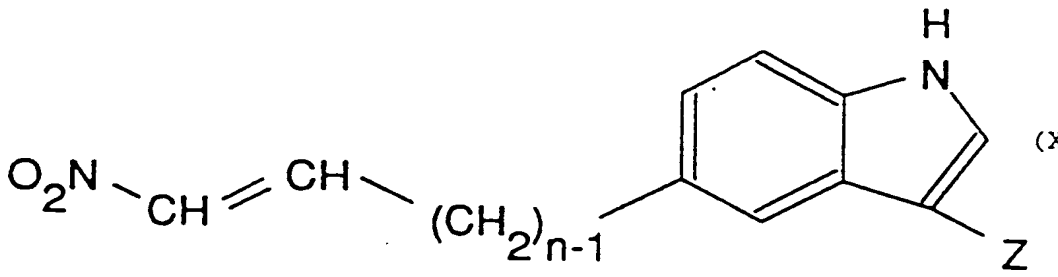
wherein n, X and Z are as hereinbefore defined, typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent, such as ethanol. The same step may be used to convert a compound of formula (XX) wherein Z is a group of formula (v) into a compound of formula (XV) wherein Z is a group of formula (vi).

Compounds of formula (XX) wherein X is oxygen may be prepared by reacting a compound of (XXI)

Compounds of formula (XXIII) may be prepared by heating the appropriate aldehyde with nitromethane in the presence of ammonium acetate. The aldehyde may be prepared from a compound of formula (XIX) wherein n is as hereinbefore defined using the reaction conditions described above for preparing a compound of formula (XVIII) from the corresponding nitrile.

Compounds of formula (XXII) wherein n = 0 may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

Compounds of formula (XXI) wherein n ≠ 0 may also be prepared from a compound of formula (XXXIX)

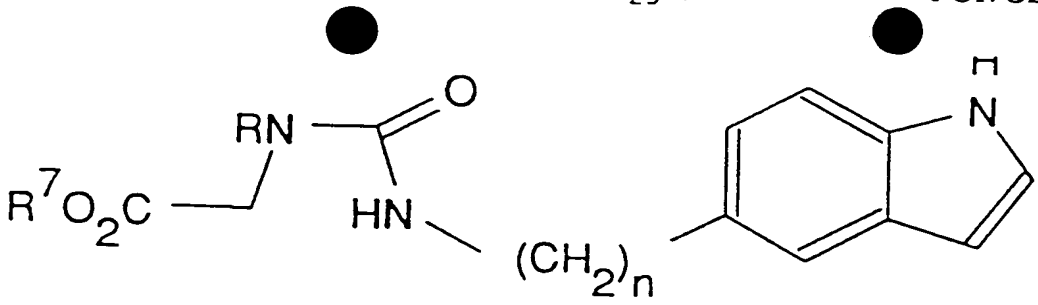


(XXXIX)

wherein n and Z are as hereinbefore defined, using reaction conditions analogous to those used to convert (XXIII) to (XXII). Compounds of formula (XXXIX) may be prepared from a compound of formula (XVIII) wherein n and Z are as hereinbefore defined using reaction conditions analogous to those used to prepare (XXIII) from the appropriate aldehyde and nitromethane.

Compounds of formula (XX) wherein X is other than oxygen may be obtained commercially or prepared from readily available starting materials by methods known to those skilled in the art or obtainable from the chemical literature.

Compounds of formula (XXV) may be prepared by ring-opening a compound of formula (I) wherein n and Z are as hereinbefore defined and W is a

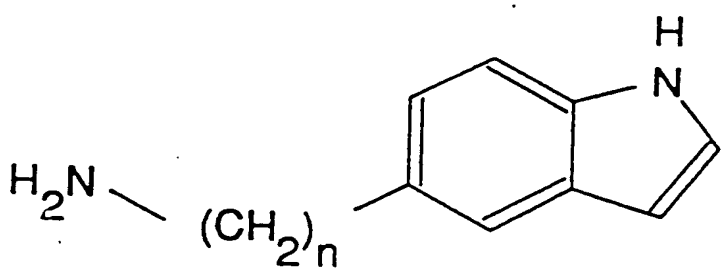


(XXVII)

wherein n, R and R^7 are as hereinbefore defined, with a compound of formula (XXVIII) wherein R^3 is as hereinbefore defined, typically by heating in a non-aqueous acid, for example, glac. acetic acid.

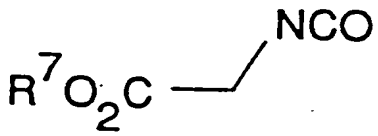
Compounds of formula (XXVI) wherein Z is a group of formula (vi) may be prepared by reducing a compound of formula (XXVI) wherein Z is a group of formula (v), typically by catalytic hydrogenation using, for example, Pd/C in a polar solvent system, such as acidified methanol/water.

Compounds of formula (XXVII) may be prepared by reacting a compound of formula (XXIX)



(XXIX)

wherein n is as hereinbefore defined, with a compound of formula (XXX)



(XXX)

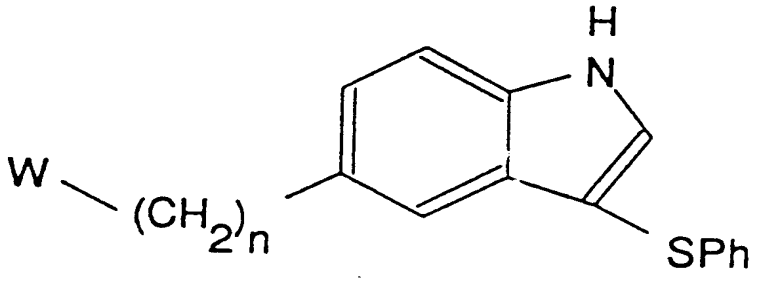
wherein R^7 is as hereinbefore defined, typically in an aprotic solvent, such as DCM.

wherein n and W are as hereibefore defined, typically by refluxing in an aprotic solvent, such as chloroform, in the presence of polyphosphate ester.

Compounds of formula (XXXX) may be prepared by reacting a compound of formula (II) wherein n and W are as hereinbefore defined with 3-cyanopropanal, or a carbonyl-protected form thereof, such as the diethyl acetal, typically in an aqueous acid, for example, dil. HCl.

Compounds of formula (I) wherein Z is a group of formula (v) may also be prepared by reacting a compound of formula (XXXI) wherein n and W are as hereinbefore defined, with a compound of formula (XXVIII) wherein R^3 is as hereinbefore defined, typically by heating in glac. acetic acid.

Compounds of formula (XXXI) may be prepared by reducing a compound of formula (XXXII)



(XXXII)

wherein n and W are as hereinbefore defined, typically by heating with Raney nickel in a polar solvent, such as IPA.

Compounds of formula (XXXII) may be prepared by reacting a hydrazine of formula (II) wherein n and W are as hereinbefore defined with phenylthioacetaldehyde, or a carbonyl-protected form thereof, for example, the diethyl acetal, in a polar solvent, such as acidified ethanol.

Compounds of formula (I) wherein Z is group of formula (vi) may also be prepared by reducing a compound of formula (I) wherein Z is a group

(c) (S)-4-(4-Nitrobenzyl)-1,3-oxazolidin-2-one

The product from step (b) (4.9g) was suspended in toluene, the suspension cooled to 0°C and a solution of potassium hydroxide (7.0g) in water (56ml) added dropwise. A solution of phosgene (62.5ml of a 12% w/v solution in toluene) was added dropwise to the resulting solution over 30 minutes and stirring continued for 1 hour. The mixture was extracted with ethyl acetate and the extracts washed with brine, dried and evaporated in vacuo to give a yellow oil. Crystallisation from ethyl acetate gave the desired product as pale yellow crystals (2.3g).

(d) (S)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one hydrochloride

A suspension of the product from step (c) (0.79g) and 10% palladium on carbon (0.26g) in a mixture of ethanol (15ml), water (11ml), ethyl acetate (2.0ml) and aqu. 2N HCl (2.3ml) was stirred under 1 atmos. pressure of hydrogen until uptake ceased. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a pale yellow foam (0.79g).

(e) (S)-4-(4-Hydrazinobenzyl)-1,3-oxazolidin-2-one hydrochloride

The product from step (d) (0.79g) was suspended in water (4.8ml) and c.HCl (8.1ml) added dropwise. The resulting mixture was cooled to -5°C and a solution of sodium nitrite (0.24g) in water (2.4ml) added dropwise to the stirred mixture over 15 minutes followed by 30 minutes' stirring at -5 to 0°C. The solution was then added at 0°C over 15 minutes to a stirred solution of tin (II) chloride (3.8g) in c.HCl (6.9ml), followed by 3 hours' stirring at room temperature. The solution was evaporated in vacuo and the residue triturated with ether to give the desired product as a pale yellow solid (0.96g).

and glac. acetic acid (0.14g) and the resulting mixture stirred overnight at room temperature. The pH was adjusted to 8.0 using aqu. K_2CO_3 and the mixture extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated to give a colourless oil (0.14g) which crystallised from isopropanol to give the desired product as a white crystalline solid (0.10g), mp 139-141°C.

^{1}H NMR (DMSO-d_6, δ): 2.2 (6H, s, $N\underline{Me}_2$), 2.5 (2H, m, $C\underline{H}_2Ar$), 2.7-3.0 (4H, m, $C\underline{H}_2$), 4.1 (2H, m, $C\underline{H}_2O$), 4.3 (1H, m, C<u>H</u>), 6.9 (1H, d, Ar), 7.1 (1H, s, Ar), 7.3 (1H, d, Ar), 7.4 (1H, s, Ar), 7.7 (1H, s, N<u>H</u>CO) and 10.7 (1H, s, N<u>H</u>).

Microanalysis: C 64.26 (64.11), H 8.28 (8.34), N 12.02 (12.00)

$[\alpha]_D^{22}$ -5.79° (c = 0.5, MeOH)

<u>Salts of Synthetic Example 2</u>

<u>Maleate</u>

A solution of maleic acid (0.17g) in ethanol (5ml) was added to a solution of the free base (0.5g) in ethanol (5ml). The mixture was evaporated <u>in vacuo</u> and the resulting oil triturated with ether and methanol to give the maleate salt as a white solid which was recrystallised from ethanol (0.45g), mp 151-152°C.

<u>Hydrochloride</u>

Ethereal HCl (1.1 equivs.) was added dropwise to a stirred solution of the free base (0.35g) in methanol (1ml) at 0°C. The hydrochloride salt precipitated as an oil. The mixture was evaporated <u>in vacuo</u> and the resulting foam crystallised from isopropanol to give the desired product as a white solid (0.36g), mp 118-120°C, $[\alpha]_D^{23}$ -9.35 (c = 0.31, water).

(a) 3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indole-5-carbonitrile

5-Cyanoindole (Aldrich, 20.0g) was added to a solution of KOH (22.4g) in methanol (200ml). N-Methyl-4-piperidone (Aldrich, 40.4g) was then added dropwise and the resulting mixture refluxed for 4 hours, then cooled and poured into water. The resulting precipitate was filtered off and dried to give the desired product as a pale pink crystalline solid (32.6g).

(b) 3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indole-5-carbaldehyde

Raney nickel (ca 10g) was added to a solution of the product from step (a) (5.0g) and sodium hypophosphite (6.0g) in a mixture of water (25ml), glac. acetic acid (25ml) and pyridine (50ml) at 45°C. The resulting mixture was stirred at 45°C for 1 hour, cooled and basified to pH 9 with 0.88 NH_4OH. The mixture was filtered through Hyflo and the filtrate extracted with chloroform. The combined extracts were dried and evaporated in vacuo to give the desired product as an off-white solid which was recrystallised from ethanol (2.4g).

(c) 5-[3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indol-5-ylmethylene]-2,4-imidazolidinedione

A mixture of the product from step (b) (2.4g), hydantoin (Aldrich, 0.98g) and ammonium acetate (0.74g) in glac. acetic acid (2.4ml) was heated at 120°C for 4 hours. The mixture was cooled and the resulting precipitate filtered off and dried to give the desired product as a yellow solid (2.4g).

(g) (±)-3-[3-(1-Methyl-4-piperidyl)-1H-indol-5-yl]-2-amino-1-propanol

A solution of the product from step (f) (4.8g) in water (20ml) and ethanol (20ml) was added dropwise to a suspension of sodium borohydride (0.61g) in a mixture of water (20ml) and ethanol (20ml) at 0°C. The resulting mixture was refluxed for 3 hours, then evaporated in vacuo and the residue eluted through a silica column using DCM/EtOH/NH_4OH (30:8:1) as eluant. The eluate was evaporated in vacuo to give the desired product as a colourless foam (1.6g).

(h) (±)-3-(1-Methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole

A mixture of the product from step (g) (1.6g), diethyl carbonate (0.73ml) and potassium carbonate (0.08g) was heated at 130°C for 5 hours. The mixture was cooled, taken up in methanol and the insoluble potassium carbonate filtered off. The filtrate was evaporated in vacuo and the residue eluted through a silica colum using DCM/EtOH/NH_4OH (30:8:1) as eluant. The eluate was evaporated in vacuo and the residue recrystallised from isopropanol/ether to give the desired product as a colourless crystalline solid (1.1g), mp 191-192°C.

^1H NMR (DMSO-d_6, δ): 1.6-1.8 (2H, 2 x CHNMe), 1.8-2.1 (4H, 2 x CH_2), 2.2 (3H, s, NMe), 2.6-3.0 (2H, 2 x CHNMe; 1H, CH; 2H, CH_2Ar), 3.9-4.1 (2H, m, CH_2O), 4.2-4.4 (1H, m, CHN), 6.9 (1H, d, Ar), 7.1 (1H, d, Ar), 7.3 (1H, d, Ar), 7.4 (1H, s, Ar), 7.8 (1H, s, NHCO) and 10.7 (1H, s, NH)

(c) 5-(2-nitroethyl)-1H-indole

A solution of sodium borohydride (2.0g) and 40% w/v aqu. NaOH was added dropwise to a solution of the the product from step (b) (1.9g) in acetonitrile (55ml) at 0°C. The pH was maintained at 3-6 by periodic additions of 2N aqu. HCl. The resulting solution was stirred at 0°C for 2 hours, then diluted with water and extracted with DCM. The combined extracts were washed with brine, dried and evaporated in vacuo to give a yellow oil which was eluted through a silica column using chloroform as eluant to give the desired product as a pale yellow oil (0.78g).

(d) 3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(2-nitroethyl)-1H-indole

N-Methyl-4-piperidone (Aldrich, 4.2g) was added to a solution of the product from step (c) (2.3g) in glac. acetic acid (35ml) at 100°C. The resulting solution was heated at 100°C for 1 hour, cooled and poured into a mixture of 0.88 NH_4OH (61ml) and ice (61g). The resulting solid was filtered off, dried and recrystallised from ethanol to give the desired product as a white solid (1.6g).

(e) (±)-3-[3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-1H-indol-5-yl]-2-amino-1-propanol

Sodium methoxide (0.30g) was added to a solution of the product from step (d) (1.5g) in DMF (15ml) at 0°C. To the resulting solution was added dropwise a suspension of paraformaldehyde (0.19g) in DMF (20ml). The resulting mixture was stirred at 0°C for 1.5 hours, then poured into water and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried and evaporated in vacuo to give a yellow oil which was eluted through a silica column using DCM/EtOH/NH_4OH (50:8:1)

(a) (R)-4-(4-nitrobenzyl)-1,3-oxazolidin-2-one

A solution of D-4-nitrophenylalanine (Fluka, 53g) in dimethoxyethane (250ml) was warmed to 67°C and $BF_3.Et_2O$ (Aldrich, 37ml) added over 1 hour. The resulting solution was stirred at 67°C for 1 hour, then heated to 80°C and $BH_3.Me_2S$ (Aldrich, 40ml) added over 1 hour at 80-85°C. The resulting solution was heated at 85°C for 4 hours, then cooled and methanol (40ml) added. The solution was heated to 85°C and the solvents removed by distillation to 1/3 of the original bulk. 6N aqu. NaOH (136ml) was added to the hot solution which was then heated at 85°C for 1/2 hour, cooled and DCM (100ml) added. The solution was cooled to -15 to -20°C and a solution of trichloromethyl chloroformate (Aldrich, 18.2ml) in DCM (23ml) added at below -10°C. The pH was maintained at 9-11 by periodic additions of 6N aqu. NaOH. The resulting solution was stirred at room temperature for 1 hour, then diluted with water and extracted with DCM. The combined extracts were washed with water and brine, dried and evaporated in vacuo to give the desired product as a pale brown solid which was recrystallised from ethyl acetate to give a pale yellow solid (35g), mp 113-115°, $[\alpha]_D^{21}$ +46.47° (c = 0.56, MeOH).

(b) (R)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one hydrochloride

The product from step (a) (10.0g) was suspended in a mixture of water (120ml), ethanol (60ml) and 2N aqu. HCl (22.5ml) and 10% w/w Pd/C (1.0g) added. The mixture was stirred under 1 atmos. pressure of hydrogen for 8 hours when uptake was complete. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a colourless glass (10.3g).

Synthetic Example 7

Preparation of (R)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine

A solution of 35% w/v aqu. formaldehyde (0.3ml) in methanol (2.0ml) was added to a solution of the product from step (d) of Synthetic Example 6 (0.44g) and sodium cyanoborohydride (0.13g) in a mixture of methanol (8.5ml) and glac. acetic acid (0.51g) at 10°C and the resulting mixture stirred at room temperature for 2.5 hours. 2N aqu. NaOH (1.3ml) was added, then sodium borohydride (0.19g) followed by 2N aqu. HCl (1.3ml). The methanol was evaporated in vacuo and the remaining solution diluted with water, taken to pH 7 with solid potassium carbonate and washed with ethyl acetate. Further potassium carbonate was added to pH 11 and the solution extracted with ethyl acetate. The combined extracts were evaporated in vacuo to give the desired product as a white foam (0.45g).

Salt of Synthetic Example 7

Hydrochloride

c.HCl (0.16ml) was added dropwise to a stirred solution of the free base (0.45g) in ethanol (4.5ml) at 0°C. The mixture was evaporated in vacuo and the resulting foam triturated with ethyl acetate to give the desired product as a white solid, mp 130°C, $[\alpha]_D^{21}$ +5.15° (c = 0.77, MeOH).

Synthetic Example 8

Preparation of (S)-N,N-dimethyl-2-[5-(2-thia-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine hydrochloride

(a) (S)-N,N-Dimethyl-2-[5-(2-amino-1-propanol)-1H-indol-3-yl] ethylamine

step (c) of Synthetic Example 1 (4.4g) in dry THF (150ml). The mixture was stirred for 1.5 hours, then dimethyl sulphate (2.1ml) was added and stirring continued for a further 16 hours. More sodium hydride (0.40g) was added and stirring continued for another 2 hours. The mixture was evaporated in vacuo and the residue suspended in ethyl acetate and filtered. The filtrate was evaporated in vacuo and the residue crystallised from ethyl acetate/hexane to give the desired product as yellow crystals (3.7g), mp 146-147°C, $[\alpha]_D^{23}$ +64.5° (c = 1.0, MeOH).

(b) (S)-3-Methyl-4-(4-aminobenzyl)-2-oxazolidinone hydrochloride

A suspension of the product from step (a) (4.0g) and 10% w/w Pd/C (0.20g) in a mixture of ethanol (70ml) and dil. HCl (2N aqu. HCl (12ml) + water (55ml)) was hydrogenated at 45 psi for 1 hour. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo to give the desired product as a foam.

(c) (S)-3-Methyl-4-(4-hydrazinobenzyl)-2-oxazolidinone hydrochloride

A solution of the product from step (b) (4.1g) in water (24ml) was cooled to -5°C and c.HCl (40ml) added. A solution of sodium nitrite (1.2g) in water (12ml) was then added and stirring continued for 0.5 hour. The resulting solution was added dropwise at -5°C to a stirred solution of stannous chloride dihydrate (18.8g) in c.HCl (34ml). The resulting mixture was stirred at 0°C for 2.5 hours, then evaporated in vacuo. The residue was taken up in water, brought to pH 2.5 using 10N aqu. NaOH and filtered. The filtrate was evaporated in vacuo and the residue triturated with ethanol and filtered. The filtrate was evaporated in vacuo to give the desired product as a froth.

freeze-dried from water to give the desired product as a colourless glass, $[\alpha]_D^{22}$ +24.5° (c = 0.5, MeOH). Elemental analysis, ^{1}H NMR and MS were consistent with the proposed structure.

Synthetic Example 11

Preparation of (S)-N-benzyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine maleate 0.75 hydrate

Benzaldehyde (0.70g) was added at room temperature to a stirred solution of the compound of Synthetic Example 1 (1.7g) in ethanol (20ml). The solution was stirred for 36 hours, then sodium borohydride (0.25g) was added in portions and stirring continued for a further 2 hours. The solution was evaporated in vacuo and the residue cooled, acidified with 2N aqu. HCl, basified with sodium bicarbonate, saturated with potassium carbonate and extracted with ethyl acetate. The combined extracts were evaporated in vacuo to give an oil which was eluted through a silica column using DCM/EtOH/NH_4OH (100:8:1) as eluant to give the free base of the desired product as a yellow froth (1.6g). A portion of this (0.13g) was dissolved in ethanol (10ml), treated with a solution of maleic acid (43mg) in ethanol (1ml) and the resulting solution evaporated in vacuo. The residue was freeze-dried from water to give the desired product as a pale yellow powder (0.16g), $[\alpha]_D^{24}$ +1.4° (c = 0.5, MeOH). Elemental analysis, ^{1}H NMR and MS were consistent with the proposed structure.

Synthetic Example 12

Preparation of (S)-N-benzyl-N-methyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]ethylamine maleate hydrate

Anhy. potassium carbonate (0.34g) was added at room temperature to a solution of the free base of Synthetic Example 11 (0.45g) in DMF (8.0ml). The suspension was stirred for 0.5 hour, then a solution of dimethyl sulphate (0.17g) in DMF (2.0ml) was added and stirring

(a) (S)-3-Phenylthio-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole

Phenylthioacetaldehyde diethylacetal (JCS. Chem.Comm. 924 (1978), 9.1g) was added at room temperature to a stirred solution of the product from step (e) of Synthetic Example 1 (9.8g) in a mixture of ethanol (150ml) and water (100ml). c.HCl (5 drops) was added and the mixture stirred at room temperature for 2 days, then partially evaporated in vacuo. The resulting aqueous suspension was extracted with ethyl acetate and the combined extracts washed with water and evaporated in vacuo to give a brown oil. The latter was eluted through a silica column using DCM/EtOH/NH_4OH (150:8:1) as eluant to give the desired product as a pale yellow oil (5.0g).

(b) (S)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole

Raney nickel (3.0g) was added to a solution of the product from step (a) (3.1g) in IPA (150ml) and the suspension refluxed for 1 hour. More Raney nickel (2.0g) was added and refluxing continued for a further 2 hours. The suspension was filtered hot through Hyflo and the filtrate evaporated in vacuo to give an oil. The latter was eluted through a silica column using ethyl acetate as eluant to give the desired product as a froth (1.3g). ^1H NMR and MS were consistent with the proposed structure.

(c) (S)-3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole 0.33 methanolate 0.75 hydrate

1-Methyl-4-piperidone (0.47g, Aldrich) was added to a stirred solution of the product from step (b) (0.30g) in glac. acetic acid (2.0ml) and the mixture stirred at 100°C for 2 hours. The cooled mixture was poured onto ice/NH_4OH (20ml) and the resulting solid filtered off. The latter was eluted through a silica column using DCM/EtOH/NH_4OH (60:8:1) as eluant and

(b) (R)-3-(1-Methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(2-oxo-1,3-oxazolidin-4-yl)-1H-indole hydrate

By steps analogous to steps (a) to (c) of Synthetic Example 14, the product from step (a) was converted to (R)-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole hydrate, mp 229-231°C, $[\alpha]_D^{18}$ +24.9° (c = 0.5, 1N aqu. HCl). Elemental analysis and ^{1}H NMR were consistent with the proposed structure.

Synthetic Example 17

Preparation of (R)-3-(1-methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole hydrobromide

By a method analogous to that of Synthetic Example 15, the product of Synthetic Example 16 was converted to (R)-3-(1-methyl-4-piperidyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole hydrobromide, mp 260-261°C, $[\alpha]_D^{19}$ +4.6° (c = 0.5, water). Elemental analysis and ^{1}H NMR were consistent with the proposed structure.

Synthetic Example 18

Preparation of (R)-3-(1-benzyl-1,2,3,6-tetrahydro-4-pyridyl)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole hydrate

1-Benzyl-4-piperidone (Aldrich, 2.8g) was added to a stirred suspension of (R)-5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indole (1.0g), the immediate precursor of the product of Synthetic Example 16, in glac. acetic acid (20ml) and stirred at 100°C for 3 hours. The cooled mixture was evaporated in vacuo and the residue taken up in methanol, basified with NH_4OH and evaporated in vacuo to give a dark tar. The latter was eluted through a silica column using DCM/EtOH/NH_4OH (100:8:1) as eluant and treated with DCM. The resulting precipitate was filtered off to give the desired product as

Synthetic Example 21

Preparation of (±)-N,N-dimethyl-2-[5-(2-oxo-2,3-oxazolidin-5-ylmethyl)-1H-indol-3-yl]ethylamine hydrochloride

(a) (±)-1-Nitromethyl-2-phenylethanol

Sodium methoxide (1.1g) was added to a stirred solution of nitromethane (Aldrich, 12.2g) in methanol (100ml) at 0°C and the mixture stirred for 10 minutes. A solution of phenylacetaldehyde (Aldrich, 24.0g) in methanol (50ml) was added dropwise over 15 minutes and the mixture stirred for 45 minutes at 0°C, then brought to room temperature over 1 hour and stirred overnight. The mixture was evaporated in vacuo and the residue taken up in water and extracted with ether. The combined extracts were washed with water and brine and evaporated in vacuo to give the desired product as a yellow oil (29.0g).

(b) (±)-1-Aminomethyl-2-phenylethanol hydrochloride

A suspension of the product from step (a) (10.0g) and 10% w/w Pd/C (1.0g) in ethanol (250ml) was hydrogenated until uptake ceased. The mixture was filtered through Hyflo and the filtrate evaporated in vacuo. The residue was taken up in ethyl acetate and extracted with 2N aqu. HCl. The combined extracts were washed with ethyl acetate, then evaporated in vacuo to give the desired product as a pinkish white solid (6.8g).

(c) (±)-5-Benzyl-1,3-oxazolidin-2-one

A solution of KOH (9.4g) in water (85ml) was added to a stirred solution of the product from step (b) (5.1g) in toluene (150ml) at 0°C. A solution of phosgene (9.8g) in toluene (78.4ml = 12.5% w/v) was added dropwise over 15 minutes and the mixture brought to room temperature, then stirred overnight. The

evaporated in vacuo. The residue was taken up in water (30ml), brought to pH 2.5 using 10N aqu. NaOH and the precipitated salts filtered off. 4-Dimethylaminobutanal diethylacetal (Croatica Chemica Acta 36, 103 (1964), 1.1g) followed by 'Amberlyst 15' ion exchange resin (Aldrich, 3.0g) was added to the filtrate and the mixture heated for 3 hours at 100°C, filtered and the filtrate evaporated in vacuo. The residue was treated with hot ethanol, filtered and the filtrate evaporated in vacuo. The residue was triturated with ethyl acetate, filtered and the filtrate evaporated in vacuo. The residue was recrystallised from ethanol to give the desired product as a pale yellow solid (0.75g), mp 280-281°C. ^{1}H NMR and MS were consistent with the proposed structure.

Synthetic Example 22

Preparation of (S)-N,N-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

(a) (S)-5-(4-Nitrobenzyl)-1,3-imidazolidin-2,4-dione

Benzyl isocyanate (Aldrich, 3.2g) was added to a solution of L-4-nitrophenylalanine (Aldrich, 4.2g) and potassium hydroxide (1.3g) in water (40ml) at 0°C. The mixture was heated at 60-70°C for 2 hours, filtered and the filtrate acidified with c.HCl to give and off-white solid which was filtered off, suspended in 2N aqu. HCl (20ml) and refluxed for 2 hours. The cooled mixture was diluted with water and filtered to give the desired product as a white solid (5.6g).

(b) (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

By steps identical to steps (d) to (f) of Synthetic Example 1 and Synthetic Example 2 or steps (d) and (e) of Synthetic

with ethyl acetate and the combined extracts evaporated in vacuo to give the desired product as a pale yellow oil (1.8g).

(d) (S)-N,N-Dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1H-indol-3-yl]ethylamine

A suspension of the product from step (c) (1.3g) and 10% w/w Pd/C (1.0g) in 30% w/w ethanolic dimethylamine (25ml) was hydrogenated for 24 hours and filtered through Hyflo. Fresh Pd/C (0.7g) and ethanolic dimethylamine (5ml) were added to the filtrate and hydrogenation continued for a further 16 hours. The mixture was filtered through a silica column using DCM/EtOH/NH_4OH (40:8:1) as eluant to give the desired product as a colourless foam (0.3g). Elemental analysis and ^1H NMR were consistent with the proposed structure.

Synthetic Examples 24 to 31

By methods analogous to those described in Synthetic Examples 1 to 23, the following compounds of formula (I) were prepared. The NMR and microanalysis for each compound were consistent with the proposed structure.

24) 2-[5-(3-Methyl-2-oxoimidazolidin-4-ylmethyl)-1H-indol-3-yl]-ethylamine maleate 0.75 hydrate, mp 94-98°C;

25) 2-[5-(3-Methyl-2-oxoimidazolidin-4-ylmethyl)-1H-indol-3-yl]-N,N-dimethylethylamine maleate 0.95 hydrate (white lyopholate);

26) 2-(5-[2-(2,5-Dioxoimidazolidinyl)ethyl]-1H-indol-3-yl)ethylamine hydrochloride hydrate, mp 83-85°C;

27) 2-(5-[2-(2,5-Dioxoimidazolindinyl)ethyl]-1H-indol-3-yl)-N,N-dimethylethylamine maleate hydrate (pale yellow lyopholate);

(ii) Sublingual

	Mg/tablet	
	D	E
Active ingredient	25	25
Avicel	10	-
Lactose	-	36
Mannitol	51	57
Sucrose	-	3
Acacia	-	3
Povidone	3	-
Magnesium stearate	1	1
	90	125

Formulations A to E may be prepared by wet granulation of the first six ingredients with the povidone, followed by addition of the magnesium stearate and compression.

(iii) Buccal

	Mg/tablet
Active ingredient	25
Hydroxypropylmethyl cellulose (HPMC)	25
Polycarbophil	39
Magnesium stearate	1
	90

The formulation may be prepared by direct compression of the admixed ingredients.

dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

(iii) Controlled release

	Mg/capsule
Active ingredient	25
Avicel	123
Lactose	62
Triethylcitrate	3
Ethyl cellulose	12
	225

The formulation may be prepared by mixing and extruding the first four ingredients and spheronising and drying the extrudate. The dried pellets are coated with ethyl cellulose as a release controlling membrane and filled into two-part, hard gelatin capsules.

(3) Intravenous injection formulation

	% by weight
Active ingredient	2%
Hydrochloric acid)	q.s. to pH 7
Citrate buffer)	
Water for Injections	to 100%

The active ingredient is taken up in the citrate buffer and sufficient hydrochloric acid added to affect solution and adjust the pH to 7. The resulting solution is made up to volume and filtered through a micropore filter into sterile glass vials which are sealed and oversealed.

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and made up to the required volume with purified water.

(7) Suppository formulation

	Mg/suppository
Active ingredient (63μm)*	50
Hard Fat, BP (Witepsol H15 - Dynamit NoBel)	1950
	2000

* The active ingredient is used as a powder wherein at least 90% of the particles are of 63μm diameter or less.

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200μm sieve and mixed with the molten base using a Silverson mixer fitted with a cutting head until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogenous mix. The entire suspension is then passed through a 250μm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.0g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(8) Pessary formulation

	Mg/pessary
Active ingredient (63μm)	50
Anhydrous dextrose	470
Potato starch	473
Magnesium stearate	473
	1000

the $p[A_{50}]$ ($-\log_{10}[M]$, where M is the molar concentration of agonist required to produce half the maximum effect). The results obtained for the compounds of Synthetic Examples 2/3 and 4/5 are shown in Table 1.

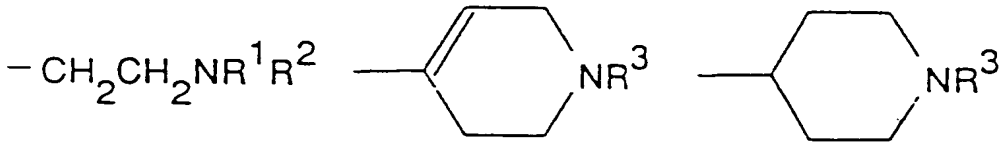
Table 1

Example	Activity $p[A_{50}]$
2/3	7.0
4/5	6.3

TOXICITY DATA

The hydrochloride salt of the compound of Synthetic Examples 2/3 was administered orally by gavage to Wistar rats as a solution in distilled water at dosages of 25, 100 and 200mg/kg base and to Beagle dogs at dosages of 0.25, 0.50, 1.0 and 2.0mg/kg base once a day for 14 days. In a separate dog study over 30 days, the dosage of the free base was increased from 2mg/kg on Day 1 to 100mg/kg on Day 30. The free base was also administered orally to cynomolgus monkeys at a dosage of 50mg/kg once a day for 15 days.

No evidence of toxicity was observed in any of the aforementioned studies at any of the dosages used.



(iv) (v) (vi)

wherein R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl and R^3 is hydrogen or C_{1-4} alkyl;

and salts, solvates and physiologically functional derivatives thereof.

2. A compound of formula (I) as shown in Claim 1, wherein

n is 1, or

W is a group of formula (i), or

Z is a group of formula (iv) or (vi),

and physiologically acceptable salts, solvates and physiologically functional derivatives thereof.

3. A compound of formula (I) as shown in Claim 1, wherein

n is 1,

W is a group of formula (i) wherein R is hydrogen, X is -O- and Y is oxygen, and

Z is a group of formula (iv) or (vi) wherein R^1 = R^2 = hydrogen or methyl.

9. Use of a compound of formula (I) as claimed in any of Claims 1 to 5, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

10. Use of a compound of formula (I) as claimed in any of Claims 1 to 5, or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, in the manufacture of a medicament for the prophylaxis or treatment of migraine.

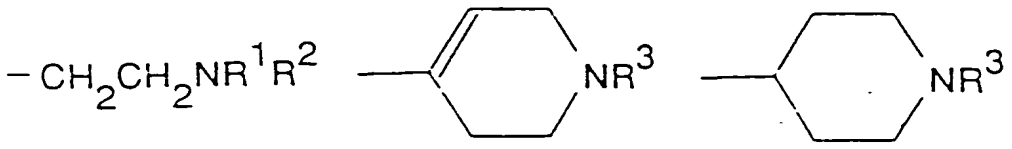
11. A method for the prophylaxis or treatment of a clinical condition in a mammal which comprises the administration to said mammal of a therapeutically effective amount of a compound of formula (I) as claimed in any of Claims 1 to 5 or of a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

12. A method as claimed in Claim 11 for the prophylaxis or treatment of a clinical condition for which a "5-HT_1-like" receptor agonist is indicated.

13. A method as claimed in Claim 12 for the prophylaxis or treatment of migraine.

14. A method as claimed in any of Claims 11 to 13 wherein said mammal is a humman.

15. A medicament comprising a compound of formula (I) as claimed in any of Claims 1 to 5 or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

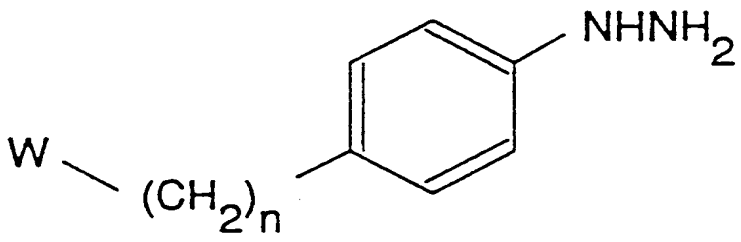


(iv) (v) (vi)

wherein R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl and R^3 is hydrogen or C_{1-4} alkyl;

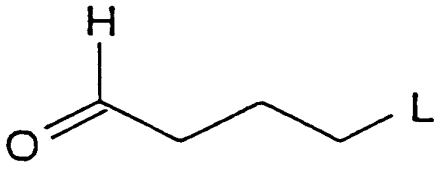
which comprises

(a) in the case where Z is a group of formula (iv), reacting a compound of formula (II)



(II)

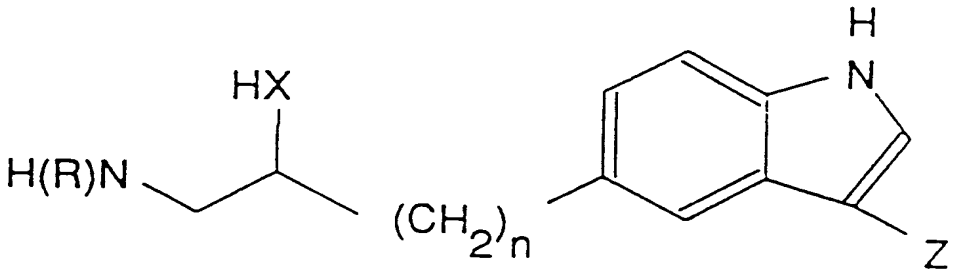
wherein n and W are as hereinbefore defined, with a compound of formula (III)



(III)

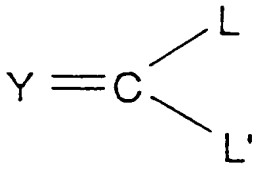
or a carbonyl-protected form thereof, wherein L is a suitable leaving group or protected amino group which may be

or (XXV)



(XXV)

wherein n, R and X are as hereinbefore defined and Z is a group of formula (vi), with a compound of formula (VII)



(VII)

wherein Y is as hereinbefore defined and L and L', which may be the same or different, are suitable leaving groups,

and optionally converting the compound of formula (I) so formed to a corresponding salt, solvate, or physiologically functional derivative.

18. A method of preparing a medicament which comprises

(a) preparing a compound of formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof by a process as claimed in Claim 17; and

(b) admixing the product from step (a) with a pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/00908

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

◆According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 413/06 A 61 K 31/40 C 07 D 413/14
C 07 D 403/06 C 07 D 401/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 413/00 C 07 D 403/00 C 07 D 401/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	EP,A,0313397 (THE WELLCOME FOUNDATION LTD) 26 April 1989, see the whole document (cited in the application)	1,6-10
Y	EP,A,0354777 (GLAXO GROUP LTD) 14 February 1990, see the claims	1,6-10
Y	EP,A,0303506 (GLAXO GROUP LTD) 15 February 1989, see the claims	1,6-10
Y	GB,A,2186874 (GLAXO GROUP LTD) 26 August 1987, see the claims	1,6-10

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02-09-1991	24. 09. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. Pez

Form PCT/ISA/210 (second sheet) (January 1985)